IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Amir BARZILAY	Confirmation No.:
Application No.: 10/561,541	Group Art Unit: 1612
Filing Date: Dec. 19, 2005	Examiner: Snigdha Maewall
For: BIOACTIVE COMPOUND PROTECTION METHOD AND COMPOSITION CONTAINING SAME	Attorney Docket No.: 15872.091

DECLARATION OF DR. LORA ESHKAR-SEBBAN UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Dr. Lora Eshkar Sebban, declare that:

1. I am a citizen of Israel and reside at 23a Hayinav St., Beit HaShmonai Israel.

2. I hold a Ph.D. in Immunology from The Hebrew University of Jerusalem, and a B.Sc. from Tel-Aviv University. My Ph.D. thesis focuses on the involvement of Galectin -8, a novel proapoptotic ligand of CD44 in joint inflammation of rheumatoid arthritis.

3. I am presently Analytical Manager at Nutrinia Ltd., a biotech company developing next generation health-promoting supplements for infant formulas. The Company is currently focused on supplementing pre-term and term infant formulas with insulin, which is present in natural mother's milk, but absent from infant formulas originated from powdered cow's milk and soy. I have published 4 papers in peer-reviewed scientific journals (a list attached as Appendix I hereinbelow). Prior to this I served as Academic Officer in the Biology and Radiology Section at Home Front Command of the Israel Defense Force.

4. I have reviewed and I understand the above-identified patent application, the full file and presently amended claims and the Office Actions, in particular the Examiner's rejection under 35 U.S.C. §103(a) of claims 117 and 119 as being unpatentable over U.S. Patent No. 5,013,569 to Rubin ("Rubin") in view of U.S. Patent No. 5,531,989 to Paul ("Paul") and of Claims 106-107 and 116-120 as being unpatentable over U.S. Patent No. 6,482,517 to Anderson ("Anderson") and U.S. Patent No. 6,048,562 to Mandralis et al. ("Mandralis et al."). I am making the following statements as one of ordinary skill in the art in support of the patentability of the presently amended claims.

5. The above-identified application as reflected in the currently pending claims is directed to a method for improving the health status of a newborn mammal by oral delivery of food or feed formulation comprising insulin encapsulated by the method of the invention, such that the activity of the insulin is substantially maintained, thereby improving the health status of the mammal as exemplified in the present invention. Specifically, as set forth in claim 106, the encapsulation step comprises the steps of (a) mixing the with an encapsulating material, wherein said encapsulating material is food-grade or feed-grade materials, either alone or in combination, with a liquid, forming a liquid blend; (b) drying the liquid blend forming a dry blend; (c) coating the dry blend with at least one additional encapsulating layer; (d) mixing the dry blend with at least one additional food-grade or feed-grade material; and (e) adding the dry blend to the mammalian newborn formulation, wherein the steps of admixing all of the ingredients and drying are conducted at a temperature below 50°C, such that the activity of the insulin is substantially maintained.

6. As one skilled in the art, based on my review of the application, of the office actions, and of Rubin, Paul, Anderson and Mandralis et al., it is my opinion and judgment that the method as set forth in currently presented claims 106-107 and 120 is not made obvious by these references.

7. Insulin in an important therapeutic protein due to its role in the treatment of diabetes, and the oral route for administering insulin is recognized as the natural and safest route of administration. Yet, the oral route continues to be a challenge to deliver proteins, and various barriers must be overcome to obtain adequate bioavailability. According to the teachings of the present invention insulin must keep its activity within the

gastrointestinal tract when administered orally. Naturally, the preparation of the feed or food formulations should not involve any steps that may cause significant insulin degradation or loss of activity. In contrast to insulin, the bioactive compounds used for restoring and maintaining gastrointestinal benefits according to Paul are immunoglobulins and dietary fibers, which are not referred to as sensitive ingredients that should be encapsulated or otherwise protected when prepared as a feed formula.

8. It is well known to a person skilled in the art that proteins and peptides undergo loss of activity following encapsulation during their processing (see, for example, Elsyed A. et al., 2009. Eur. J. Pharmac. Biopharmac. 73:269-279). Thus, general reference to the need to encapsulate a protein for delivery, as disclosed in Rubin (column 4, lines 58-68) does not provide any guidance, let alone particular method as to how to encapsulate insulin such that its activity would be preserved during the encapsulation process and via oral administration to exert its activity on the gastrointestinal tract.

Anderson teaches a method of making a particle coated with a nanolamellar crystalline material including an internal core of liquid phases and active ingredient. Anderson provides a large number of examples of particular methods for producing the coated particles and their use for encapsulating various active ingredients. However, the methods described are significantly different from the encapsulation method disclosed in the present invention and/or are not suitable for encapsulating of insulin for oral delivery according to the teachings of the present invention. In several examples, heating steps to above 50°C (typically to the range of 100-120°C) are included, which would result in insulin degradation. Sonication for about 2-3 hours will most likely result in insulin degradation. In several examples (e.g., 4, 5, 14-16, 23 34-36 and 38) hazardous compound or compounds which are not suitable for oral consumption are used. In other example, no active ingredient was encapsulated, and/or the active ingredient was the coating material, and thus the methods described are not relevant to the present invention (examples 22, 25, 29-31). Furthermore, nowhere in Anderson is the use of the encapsulation protocols for efficient delivery of sensitive ingredient like insulin is exemplified.

Mandralis et al. use high pressure and a temperature of up to 100°C which would cause insulin degradation.

As acknowledged by the Examiner, none of the above references shows that the encapsulation methods disclosed provide the desired protective effect when the encapsulated material is administered orally within a feed or food formula. As of today, to my best ability to ascertain, there is no available formula for oral delivery of insulin shown to

be effective in promoting the health status of a newborn mammal, including at least one of increasing the rate of weight gain of said mammals, preventing diarrhea and other gastric disorders and increasing the life expectancy of said mammals after birth.

9. Based on the foregoing, it is thus my opinion and judgment, as one of skill in the art, that the combination of the teachings of Rubin, Paul, Anderson and Mandralis et al. does not make the method of currently pending claims 106-107 and 120, directed towards a method for improving the health of a mammal, obvious to one skilled in the art, as none of these references provide data as to the efficacy of the encapsulation methods in protecting insulin such that it will exert its bioactivity after being administered orally.

10. I further declare that all statements made herein of my knowledge are true and all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Dated: 6 July 2010

LORA ESHKOL SEBBAN

Lora Eshkar Sebban, Ph.D.

Appendix I

Publication List Dr. Lora Eshkar Sebban

- **Eshkar Sebban L**, Ronen D, Levartovsky D, Elkayam O, Caspi D, Aamar S, Amital H, Rubinow A, Golan I, Naor D, Zick Y, Golan I. The involvement of CD44 and its novel ligand galectin-8 in apoptotic regulation of autoimmune inflammation. J Immunol. 2007 Jul 15;179(2):1225-35.
- Golan I, Nedvetzki S, Golan I, **Eshkar-Sebban L,** Levartovsky D, Elkayam O, Caspi D, Aamar S, Amital H, Rubinow A, Naor D. Expression of extra trinucleotide in CD44 variant of rheumatoid arthritis patients allows generation of disease-specific monoclonal antibody. J Autoimmun. 2007 Mar-May;28(2-3):99-113. Epub 2007 Mar 23.
- Naor D, Nedvetzki S, Walmsley M, Yayon A, Turley EA, Golan I, Caspi D, **Eshkar Sebban L**, Zick Y, Garin T, Karussis D, Assayag-Asherie N, Raz I, Weiss L, Slavin S, Golan I. CD44 involvement in autoimmune inflammations: the lesson to be learned from CD44-targeting by antibody or from knockout mice. Ann N Y Acad Sci. 2007 Sep;1110:233-47. Review.
- Naor D, Nedvetzki S, Golan I, **Melnik L**, Faitelson Y. CD44 in cancer. Crit Rev Clin Lab Sci. 2002 Nov;39(6):527-79.